REMARKS

Claims 1-7, 35-40, and 41-50 are pending. Claims 4 and 40 are amended, finding support in the specification at least in paragraph **[0004]**. New claim 51 is submitted, which finds support at least in the original claims. New claims 52 and 57-61 finds support in the application at least at paragraphs **[0244]-[0246]** and paragraph **[0273]**. New claims 53-56 find support in the specification at least at paragraph **[0062]**.

Regarding the Examiner's decision to maintain the election of one SEQ ID NO and also to refrain from classifying the restriction as a species election, Applicants reiterate their strong objection to this wholly unreasonable assessment of the invention elements. Applicants are aware of the rules pursuant to 35 U.S.C. §121 that if two or more independent and distinct inventions are claimed in a single application, then election of restricted inventions is required. However, Applicants assert that contrary to the Examiner's assessment that the nucleotide sequences are unrelated to one another and constitute independent and distinct inventions within the meaning of 35 U.S.C. §121, the sequences listed in original claim 3 are NOT unrelated to one another as they are merely distinct and often overlapping regions of the same polynucleotide---a periaxin polynucleotide. ***If these are not a classic definition of species members of a genus, then just what IS a species?***

The Merriam-Webster Dictionary of Law (© 1996 Merriam-Webster, Inc.) defines independent as "not affiliated with another usually larger unit," and multiple permutations of the same periaxin polynucleotide are certainly affiliated with one another. Furthermore, Applicants note in MPEP §803 that restriction is proper when the inventions are independent or distinct as claimed AND there must be a serious burden on the Examiner to do the searches. Applicants consider for this particular case having highly similar periaxin sequences that the searches would not impart an undue burden for the Examiner and that the election is wholly unreasonable. ***This is particularly true for this case, given the analogous instances wherein a partial waiver of 37 CFR §1.141 is proper for highly related nucleotide sequences, as described in MPEP §803.04; given that these sequences are variations of the same periaxin polynucleotide, and they in many ways contain structural similarity, the rule is clearly applicable to the presently pending claims.***

Applicants respectfully request reconsideration of the final restriction by the Examiner.

I. Issues under 35 U.S.C. 112, first paragraph

Claims 1-7, 35-40 and 42-50 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicants respectfully disagree. The pending claims are enabled, as the disclosure teaches a variety of mutations associated with myelinopathies, such as DSN, and Applicants do in fact teach a skilled artisan how to make and use the invention in a manner commensurate with the claims. ***Applicants emphasize that the pending independent Claims 1, 35, 43, and new claim 57 require that the myelinopathy results from or is associated with a periaxin alteration.*** Therefore, these pending claims do not cover myelinopathies resulting from other mutations, and the scope is not so broad as the Examiner contends.

The Examiner also alleges that the specification has not established a predictable correlation between any mutation in the periaxin gene and any myelinopathy or any specific myelinopathy. The predictable correlation is that the defect in a periaxin polynucleotide is associated with a myelinopathy, and myelinopathies are each units of a spectrum of closely related diseases. Applicants are not trying to claim periaxin for a wide range of diseases but those as part of a phenotypically narrow range of myelinopathies. The specification states in paragraph **[0263]**: "The association of mutations in *PRX* with peripheral neuropathy not only identifies another genetic cause for the *CMT1 spectrum of myelinopathies* but also provides further insights into the molecular mechanisms *for these diseases*." (emphasis added)

Furthermore, Applicants note that multiple papers since the filing of the application teach periaxin alterations that are associated with myelinopathies other than DSN. For example, Guilbot *et al.* (2001) teach that periaxin is responsible for an autosomal recessive form of CMT disease; in fact, Guillot published approximately two months after the filing of Applicants' provisional application. Also, Kijima *et al.* (2004) determined that periaxin mutation causes early onset CMT. ***Given that Applicants taught in the original disclosure that alterations in periaixin are indicative of myelinopathies, these subsequent papers indicate that Applicants in fact did provide how to make and use the invention, and the claims are thus enabled.*** This is particularly valid given that, as noted above, independent claims 1, 35, 43, and 57 require that the myelinopathy results from or is associated with a periaxin alteration.

The Examiner also states in the Office Action that the specification has not established that a statistically significant association exists between all of the specific mutations disclosed in the specification and any myelinopathy or that a predictable correlation can be made as to an association between any mutation in the periaxin gene and any myelinopathy. Applicants reiterate that it is not required to provide stastistically significant data for enablement of a claim; this is simply not the standard required by the USPTO. The scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants assert that a reasonable correlation certainly does exist, given that *PRX* shown with DSN and the highly related myelinopathies are within the scope of reasonable correlation, particularly given their art-recognized phenotypic similarities. Furthermore, given that others subsequently identified periaxin mutations in myelinopathies of the spectrum other than DSN and commensurate with Applicants' teaching, there is most certainly a reasonable correlation. Thus, the Examiner is inappropriately requiring statistically significant data for enablement of a claim.

The Examiner further states that the scope of the claims be commensurate with the teachings in the specification and alleges that in the instant case the specification teaches PRX mutations that are not associated with myelinopathy in general or any of the specific myelinopathies. However, Applicants reiterate that this is NOT what the cited sections teach.

The ending of paragraph **[0244]** states:

> The unaffected parents and son of family HOU579 are each ***heterozygous carriers of a PRX mutant allele*** (FIG. 3). Families HOU418, HOU579 and HOU297 exhibit autosomal recessive inheritance. Black symbols indicate DSN. Patient 851 from family HOU297 is compound heterozygous for mutations S929fsX957 and R953X; her older normal son is heterozygous for R953X. Patient 1461 from family HOU579 is compound heterozygous for mutations V763fsX774 and R368X; her normal brother is heterozygous for V763fsX774. Patient 1136 from family HOU418 has the homozygous mutation S929fsX957; her two normal sisters and her son are heterozygous for this mutation. (emphasis added)

The Examiner misconstrues this passage by saying that it teaches PRX mutations are not associated with myelinopathy. This teaches that individuals can be carriers for the

mutation for the disease by being heterozygous for the mutation; this is absolutely classical genetics and does not indicate that PRX mutations are NOT associated with myelinopathies.

Regarding Table 2 on page 67 of the application, however, these sequence alterations merely represent benign polymorphic variants, which are common in human genetics. Upon being presented with a sequence alteration, a skilled artisan would know how to identify them as disease-causing of specific myelinopathies, given the level of skill in the art and presence of sufficient working examples in the disclosure and the art. With the Response to the previous Office Action, filed December 18, 2003, Applicants submitted a factual declaration under 37 CFR §1.132 to show that one skilled in the art would be able to make and use the claimed invention using the application as a guide. The affidavit by co-inventor Dr. James Lupski filed with the Response to Office Action on December 18, 2003, states as follows:

> The Examiner also expresses concern about the unpredictability of identifying whether a sequence variation is a polymorphism or a disease-causing mutation, but in diseases such as those myelinopathies that comprise an autosomal recessive nature (see, at least, paragraphs **[0062]**, **[0242]**, **[0244]**, **[0246]**, **[0247]**, **[0260]**, **[0261]**, **[0268]**, and **[0273]**), it is significant that mutations on both alleles must be present before the disease occurs, whether as a homozygote or compound heterozygote. That is, it is highly unlikely with an affected family that two non-diseased parents of a diseased individual would be carriers of the same polymorphism. In fact, if the myelinopathy had an inheritance pattern other than autosomal recessive, we would be able to easily identify this, as well.
>
> ***Moreover, a skilled artisan recognizes how to discern between a polymorphism and a disease-causing mutation. If the sequence alteration is a polymorphism, it is not identified in controls and/or does not segregate with the disease phenotype. By definition in the field of human genetics a polymorphism has to be observed in 1% of chromosomes. Thus, the absence of such a variant in 50 control normal individuals (i.e. 100 control chromosomes) is inconsistent with the variant representing a polymorphism.*** (emphasis added)

Therefore, one of skill in the art would recognize a polymorphism *vs.* a disease-causing mutation based on routine practices utilized in the art. Although the Examiner stated that the arguments and affidavit were found non-persuasive, Applicants respectfully request their reconsideration. Applicants refer the Examiner to *In re Oelrich*, 579 F.2d 86, 198 USPQ 210 (CCPA 1978) which states that the opinions of experts are based on their

competence bearing the level of ordinary skill in the art and are sufficient to shift the burden of going forward with the evidence back to the PTO. With this shift in the burden, the ***Examiner cannot dismiss a declaration without adequate explanation of why the declaration failed to overcome the rejections*** (*In re Alton*, 76 F.3d 1168, 1174 37 USPQ2d 1578, 1583 (Fed. Cir. 1996)), when in fact the affidavit specifically addressed this and other issues. Regarding the affidavit, the Examiner on page 13 of the Action merely reiterates her previously made and current arguments. Therefore, Applicants respectfully request that the Examiner reevaluate the entire application in light of the submitted declaration, arguments, and cited references enclosed therein.

The Examiner further states in the Office Action that in Example 8 there is an association of some specific PRX mutations with peripheral neuropathies and none of the mutations are specific for SEQ ID NO:76. However, Example 8 refers to identifying mutations in periaxin mRNA, of which SEQ ID NO:76 and SEQ ID NO:1 are variants of periaxin polynucleotide sequence (note Applicants' arguments above concerning the unrealistic restriction and unreasonable holding for non-consideration of these as species). Applicants are unclear in this passage about the meaning of "none of the mutations are specific for SEQ ID NO:76", when in fact it is stated:

> Sibling patients PN-44.1 and PN-44.4 were homozygous for the mutation 2145T>A that by conceptual translation causes a nonsense stop codon at amino acid 715 that normally encodes a cysteine (C715X). Patient PN-761.3 was homozygous for 247DC that results in frameshift mutation R82fsX96. The unaffected parents, sister and brothers either did not carry the mutation or were heterozygous carriers (FIG. 5). ***We did not observe either 2145T>A or 247DC in 180 control chromosomes***. (emphasis added)

The Examiner concludes on page 12 of the Action that "the specification fails to teach that all mutations of PRX, irrespective of mutation in a single allele or in two alleles, would lead to any type of myelinopathy". This is an inappropriate standard, particularly given that at least the majority of periaxin disease-causing mutations are in fact autosomal recessive, requiring two alleles to be defective. Moreover it does not address why the Examiner considers claims 49-50, which are not directed to diagnosis of myelinopathy, are not considered enabled. Nevertheless, Applicants present new claims 57 and 61 that address the carrier issue.

Applicants reiterate that undue experimentation is not required to determine which nucleotide alterations are associated with myelinopathy. The Examiner contends that a large amount of trial and error would be required to determine which mutations are associated with the disease. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cirl 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). In fact, time-consuming experiments are acceptable if the type of experimentation is standard in the art. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Yet further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985). Techniques in molecular biology are, and were at the time of the application, well known and understood in the art.

Actual reduction to practice prior to filing is not required to prove enablement (*In re Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)), and it is well-settled case law that a specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). No undue experimentation is required to make and use the invention as claimed, particularly given that Applicants provide detailed characteristics of exemplary mutations associated with DSN and related myelinopathies (such as at least in Example 8).

Even if experiments are necessary, a considerable amount of routine experimentation is permissible, especially where the Applicants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). The Office Action asserts that such experimentation is not routine, yet that argument fails to apply a standard of reasonableness to the state of the art and the relative skill of those in the art. It is well recognized "that the skill in the art of molecular biology is quite high." Id. at 548.

Furthermore, time is not a sole criterion of what constitutes undue experimentation in a particular case. Therefore, in contrast to the Examiner's assertions, the experimentation is, in fact, routine.

Applicants assert that there are a considerable number and content of working examples commensurate with the scope of the claims. For example, in Example 1 (paragraphs **[0235]** to **[0241]**, Applicants provide materials and methods to practice exemplary embodiments of the invention, including obtaining the periaxin polynucleotide, mapping it, and screening for mutations, such as by PCR. Example 2 provides characterization of the *PRX* gene, including a tissue expression profile, *in situ* hybridization by FISH, and sequencing. Example 3 provides teaching of *PRX* mutation analysis in 168 peripheral neuropathy patients who had tested negative for mutations in *PMP22, MPZ, GJB1, EGR2*, or *MTMR2*. Even though alterations in *PRX* are described for unaffected family members, it is well-known in the field how to correlate a particular mutation with a disease.

Furthermore, Example 8 shows that *PRX* mutations are related to a spectrum of demyelinating neuropathies (in paragraph **[0268]**): "These two families confirm that putative loss-of-function mutations in *PRX* cause autosomal recessive neuropathies and ***broaden the spectrum of PRX-associated peripheral neuropathies***." (emphasis added) Also (in paragraph **[0273]**): "Similar to the spectrum of phenotypes observed with mutation of other genes associated with CMT and related inherited peripheral neuropathies, the clinical phenotypes manifested in patients with mutations in *PRX* include CMT myelinopathies and DSN." As such, Applicants note that the invention has been utilized to evaluate thousands of neuropathy patients during the last few years (Athena Diagnostics).

Applicants assert that even if one could argue that the specification did not provide enough working examples, Applicants submit that examples may be either "working" or "prophetic", and compliance with the requirements for enablement under 35 U.S.C. 112 does not require that an example is disclosed, or that the invention be reduced to practice prior to filing, *Gould* v. *Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) and M.P.E.P. 2164.02. Applicants, however, strongly assert that the present Examples do comply with 35 U.S.C. §112 and the invention was reduced to practice prior to filing of the priority document.

Furthermore, the Federal Circuit has held that § 112 does not require that the applicant describe exactly the subject matter claimed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Moreover, it is not necessary that a patent applicant test all the embodiments of his invention. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Section 112 requires simply that the patent applicant provide a disclosure which sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213. The identification of exemplary mutations associated within the spectrum of myelinopathies provides a disclosure that more than sufficiently enables the scope for myelinopathies, particularly given that the ability to associate mutations with particular diseases is achieved by well-known means in the art.

It is not unpredictable for a skilled artisan to be able to determine whether or not a particular sequence variation is associated with a disease state, and furthermore, it is routine to do so. In fact, even within the CMT family itself a variety of mutations in other genes have been associated with the disease (see paragraph **[0004]**), yet Applicants remind the Examiner that pending claims 1, 35, 43, and 57 and their dependent claims regard only those myelinopathies resulting from a periaxin alteration.

In discussing claim breadth, M.P.E.P. § 2164.03 provides that:

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

M.P.E.P. § 2164.03, 2100-116 (1995). Should the Examiner feel that the present invention is directed to an art where certain results may be associated with a degree of unpredictability, M.P.E.P. § 2164.03 also supports Applicants' position on enablement rather than that advanced in the Action. M.P.E.P. § 2164.03 further provides:

> It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.

Id. (quoting *In re Dreshfield*, 45 U.S.P.Q. 36 (C.C.P.A. 1940)).

Applicants assert that they have provided ***both*** sufficient numbers of *PRX* mutations and associating myelinopathies and appropriate language enabling the invention. Although some experimentation may be involved, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The correlation between particular mutations and disease states is performed by well-known means in the art, and the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants assert that there are more than sufficient number and content of working examples provided in the specification to support association of *PRX* mutations with a range of myelinopathies within the CMT1 category, which is further supplemented by examples in the art (Boerkoel et al., 2001 (related to the instant specification); Guilbot et al., 2001; Delague et al., 2000; provided in a Supplemental Information Disclosure Statement filed herewith). Applicants teach in paragraph **[0062]** and **[0268]** that mutations in periaxin cause human peripheral myelinopathies, given that multiple unrelated DSN patients with recessive *PRX* mutations were identified as well as families associated with the spectrum of *PRX*-associated peripheral neuropathies. Applicants also provide a variety of means to obtain sequence information (paragraph **[0063]**) and a voluminous number of periaxin polynucleotide sequences (paragraph **[0064]**) to assay for mutations in an analysis.

Moreover, the specification in paragraphs **[0074]** through **[0083]** discuss different exemplary embodiments of myelinopathies having similar and overlapping phenotypes directed to at least defects in myelin, but also onion bulb defects (found in CMT1, DSN, and CHN); slowed motor nerve condution velocities (NCV) (found in CMT1, HNPP, DSN, and CHN); muscle weakness (CMT1 and CHN); gait disturbance or ataxia (CMT1 and RLS); and areflexia (CHN and RLS), for example. This is clear evidence that this is a ***group of highly related diseases having significant phenotypic overlap*** likely to associate with *PRX* defects.

Applicants assert that the minor amount of experimentation to determine if an unknown periaxin mutation associates with a myelinopathy selected from Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSN), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS) raises very little unpredictability. This is particularly true given that patients from four unrelated demyelinating neuropathy families, three manifesting DSN and one with a severe demyelinating CMT, CMT4F, have recessive *PRX* nonsense and frameshift mutations (Boerkoel et al., 2001 (related to the instant specification); Guilbot et al., 2001; Delague et al., 2000).

Thus, Applicants assert that the claims are in fact enabled and respectfully request removal of the rejection.

II. Issues under 35 U.S.C. 112, second paragraph

Claims 1-7, 35-36, and 39-40 are rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully disagree but amend claims 1, 35, and 43 herein to further the prosecution of this case.

III. Issues under 35 U.S.C. 102(a)

Claims 2-3, 38, 44-45 and 50 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Boerkoel *et al.* (2001) ("Boerkoel"). Applicants do not acquiesce as to the anticipation of the claimed invention by this reference. The provisional application filed December 13, 2000 (prior to "Boerkoel") teaches identification of alterations in the periaxin sequence of SEQ ID NO:1. Applicants acknowledge that SEQ ID NO:76 is not mentioned in the provisional application. However, SEQ ID NO:1 and SEQ ID NO:76 are splicing variants of the same polynucleotide (see FIG. 1b) wherein SEQ ID NO:1 comprises intron 6 that SEQ ID NO:76 lacks. Therefore, the periaxin polynucleotide represented in SEQ ID NO:76 is, in many respects, provided in the provisional application.

Nevertheless, Applicants submit herewith a 37 CFR §1.132 Declaration addressing this issue to remove the inventors' own reference to further the prosecution of this case. Pursuant to such, Applicants respectfully request removal of the rejection.

IV. Issues under 35 U.S.C. 103(a)

Claims 1, 4, 5, 35, 39, 40, and 49 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gillespie et al. (1997; "Gillespie"). Applicants respectfully disagree.

Gillespie merely teaches chromosomal localization of mouse periaxin and ***speculates*** as to chromosomal localization of human periaxin. Although it states in the introduction that defects in *Prx* may underlie certain human peripheral neuropathies, there is no teaching, suggestion, or motivation in Gillespie to assay a *Prx* polynucleotide in search of identifying a mutation, particularly when the references states on page 298, closing paragraph, "No human peripheral nerve demyelinating neuropathy has yet been mapped to this region."

There must be a teaching or suggestion to make the claimed limitations, and Applicants remind the Examiner that the level of skill in the art cannot be relied upon for suggestion. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Thus, Applicants assert that the Office has not established a *prima facie* case of obviousness to reject the claims under 35 U.S.C. §103. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, (Fed. Cir. 1991).

Furthermore, if the authors themselves cast doubt on the localization of human *Prx* to the region being associated with demyelinating neuropathies, why would a skilled artisan find it obvious to assay *Prx* for mutations associated with demyelinating neuropathies? This teaches away from Applicants' invention. Applicants respectfully remind the Examiner that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Thus, Applicants assert the invention is not obvious and respectfully request removal of this rejection.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response other than the fees for an Extension of Time of One Month and for a Supplemental Information Disclosure Statement. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02086US1 from which the undersigned is authorized to draw.

Dated: Aug. 25, 2004

Respectfully submitted,

By _____

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